Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 22-49, 51-53, 55-68 and 70 are pending in the application, with claims 22-23, 63-64 and 68 being the independent claims. Claim 63 is allowed by the Examiner. Claims 50, 54 and 69 are sought to be canceled without prejudice to or disclaimer of the subject matter therein. Claims 1-21 were previously canceled. Applicant reserves the right to pursue canceled subject matter in related divisional or continuation applications.

Claims 22, 23 and 68 have been amended to clarify the scope of the claims. Support for the amendment of claims 22, 23 and 68 is found, *inter alia*, at paragraph [0070], page 17 of the specification.

As requested by the Examiner, the specification has been amended to insert sequence identifiers for the nucleotide and amino acid sequences present in the specification. These amendments to the specification are the same as those made under Article 34 PCT in the corresponding International Appl. No. PCT/US03/33433.

As such, these changes are believed to introduce no new matter, and their entry is respectfully requested. Based on the above amendments and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Rejection under 35 U.S.C. § 102

The Examiner rejected claims 22-30, 33, 36-38, 41-43, 50-54, 56 and 65-70 under 35 U.S.C. § 102(e), as allegedly anticipated by Perkins *et al.* (U.S. Appl. Pub. No.

2003/0119104). Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, claims 50, 54 and 69 have been canceled and independent claims 22, 23 and 68 have been amended to specify that the genetic vectors and eukaryotic cell comprise:

> (1) distal 5' flanking sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found between 20 bp and 100,000 bp 5' of a transcriptional initiation site of a ferritin heavy chain locus;
> (2) proximal 5' regulatory sequences comprising a sequence of at least 20 bases having at least 70% identity to a nucleotide sequence found between 1 bp and 10,000 bp 5' of a translational initiation codon of a ferritin heavy chain locus; *and*
> (3) proximal 3' regulatory sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found within the proximal 3' regulatory sequences of a ferritin heavy chain gene locus.

Applicant respectfully submits that the cancellation of claims 50, 54 and 69 renders the Examiner's rejection regarding these claims moot, and respectfully requests that the rejection be withdrawn. Applicant will address the rejection in the event the Examiner may find it applicable to the remaining claims as amended.

Perkins *et al.* describes artificial chromosomes that have been engineered to contain site-specific recombination-directed integration of a DNA of interest. *See* Perkins *et al.* at Abstract. The only description in Perkins *et al.* related to the ferritin heavy chain gene is in reference to the "human Fer-1 promoter" (SEQ ID NO: 128) described as the "... [f]erritin heavy chain promoter (excluding the Iron Response Element, located in the 5' UTR), which was joined to the 37 bp Fer-1 enhancer element." *See* Perkins *et al.* at paragraph [0098]. Perkins *et al.* also describes the pMG plasmid, which does not contain the human Fer-1 promoter, as comprising a polyadenylation

signal from the bovine growth hormone gene, SV40 late polyadenylation signal, and synthetic polyadenylation site containing the AATAAA hexanucleotide sequence. *See* Perkins *et al.* at paragraphs [0314]-[0318].

As indicated at page 7 of the Office Action, Perkins *et al.* does not describe 3' regulatory regions for the ferritin heavy chain gene locus, let alone the claimed proximal 3' regulatory sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found within the proximal 3' regulatory sequences of a ferritin heavy chain gene locus. For at least these reasons, Perkins *et al.* does not disclose each and every element of the amended claims and, therefore, fails to anticipate the amended clams. As such, Applicant respectfully requests that this rejection be withdrawn.

II. Rejections under 35 U.S.C. § 103

A. Perkins et al., in view of Kwak et al.

In the Office Action at pages 4-6, claims 34, 39-40 and 44-45 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Perkins *et al.*, in view of Kwak *et al.* (J. Biol. Chem., 1995, 270:15285-15293). As described above, independent claim 22 has been amended to specify that the genetic vector comprises:

> (1) distal 5' flanking sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found between 20 bp and 100,000 bp 5' of a transcriptional initiation site of a ferritin heavy chain locus; (2) proximal 5' regulatory sequences comprising a sequence of at least 20 bases having at least 70% identity to a nucleotide sequence found between 1 bp and 10,000 bp 5' of a translational initiation codon of a ferritin heavy chain locus; *and*

> (3) proximal 3' regulatory sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found within the proximal 3' regulatory sequences of a ferritin heavy chain gene locus.

Rejected claims 34, 39-40 and 44-45 depend from claim 22 and further specify larger total lengths of the distal 5' and proximal 5' sequences. Applicant will address the rejection in the event the Examiner may find it applicable to the claims as amended.

The Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984). The factors to be considered under 35 U.S.C. § 103(a), are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and M.P.E.P. § 2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc. (KSR)*, 82 USPQ2d 1385 (2007).

The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. § 103 should be made explicit. *See id.* The Court, quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006), stated that "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR v. Teleflex*, 82 USPQ2d at 1396. As outlined in M.P.E.P. § 2141, rationales that may support a conclusion of obviousness include:

> (a) combining prior art elements according to known methods to yield predictable results;
> (b) simple substitution of one known element for another to obtain predictable results;
> (c) use of known technique to improve similar devices (method or product) ready for improvement to yield predictable results;

> (d) applying a known technique to a known device (method or product) ready for improvement to yield predictable results;
> (e) "obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
> (f) known work in the one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; and
> (g) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Applicant respectfully asserts that the Examiner has not provided an adequate reason to combine the reference teachings to arrive at the claimed invention as amended. In addition, Applicant respectfully asserts that even if the prior art references are combined, the methods do not yield predictable results, as demonstrated by the references themselves.

As described above, Perkins *et al.* does not describe 3' regulatory regions for the ferritin heavy chain gene locus, let alone the claimed proximal 3' regulatory sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found within the proximal 3' regulatory sequences of a ferritin heavy chain gene locus.

Kwak *et al.* describes that tumor necrosis factor-α (TNF-α) binds regions in the ferritin heavy chain promoter approximately 4.8-5 kb upstream of the ferritin heavy chain transcriptional start site. *See* Kwak *et al.*, page 15285, right column. Kwak *et al.* also describes that the significance of these TNF-α-responsive elements is unclear, because the TNF-α-responsive elements are in a different position than the elements

responsible for basal transcription of the ferritin heavy chain gene (which are located in the first few hundred nucleotides of the 5' flanking region). *See* Kwak *et al.*, page 15293, left column.

As such, Kwak *et al.* fails to remedy the deficiency of Perkins *et al.* because Kwak *et al.* does not describe 3' regulatory regions for the ferritin heavy chain gene locus, let alone the claimed proximal 3' regulatory sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found within the proximal 3' regulatory sequences of a ferritin heavy chain gene locus. Moreover, the combination of Perkins *et al.* and Kwak *et al.* would not yield predictable results because the regulatory sequences identified in Kwak *et al.* are responsive to an inflammatory cytokine, TNF-α, and are located in far different regions than the regulatory sequences responsible for basal transcription of the ferritin heavy chain gene.

For at least the reasons presented above, Applicant submits that a *prima facie* case of obviousness has not been established. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

B. Perkins et al., in view of Kaufman

In the Office Action at pages 6-8, claims 35, 55 and 57-62 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Perkins *et al.*, in view of Kaufman (U.S. Patent No. 4,740,461). As described above, independent claim 22 has been amended to specify that the genetic vector comprises:

> (1) distal 5' flanking sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found between 20 bp and 100,000 bp 5' of a transcriptional initiation site of a ferritin heavy chain locus;

> (2) proximal 5' regulatory sequences comprising a sequence of at least 20 bases having at least 70% identity to a nucleotide sequence found between 1 bp and 10,000 bp 5' of a translational initiation codon of a ferritin heavy chain locus; *and*
> (3) proximal 3' regulatory sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found within the proximal 3' regulatory sequences of a ferritin heavy chain gene locus.

Rejected claims 35, 55 and 57-62 depend from claim 22 and further specify larger total lengths of the proximal 3' or distal 3' sequences. Applicant will address the rejection in the event the Examiner may find it applicable to the claims as amended.

As described above, Perkins *et al.* does not describe 3' regulatory regions for the ferritin heavy chain gene locus, let alone the claimed proximal 3' regulatory sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found within the proximal 3' regulatory sequences of a ferritin heavy chain gene locus.

Kaufman describes expression vectors with a downstream polyadenylation site. *See* Kaufman at columns 7-8. Kaufman describes that such sites are "well known" and "... may be obtained from viruses in accord with published reports." *See* Kaufman at column 8, lines 6-12. Kaufman further describes that viral polyadenylation sites are preferred, and provides that exemplary polyadenylation sequences can be obtained from mouse beta-globin or simian virus 40 late or early region genes. *See* Kaufman at column 8, lines 12-15. As such, Kaufman fails to remedy the deficiency of Perkins *et al.* because it does not describe 3' regulatory regions for the ferritin heavy chain gene locus, let alone the claimed proximal 3' regulatory sequences comprising a sequence of at least 100 bases

having at least 70% identity to a nucleotide sequence found within the proximal 3' regulatory sequences of a ferritin heavy chain gene locus.

For at least the reasons presented above, Applicant submits that a *prima facie* case of obviousness has not been established. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

C. Perkins et al., in view of Eglitis et al. or Hillgenberg et al.

In the Office Action at pages 8-9, claims 46-49 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Perkins *et al.*, in view of Eglitis *et al.* (U.S. Patent No. 5,672,510) or Hillgenberg *et al.* (U.S. Patent Appl. Pub. No. 2002/0001579). As described above, independent claim 22 has been amended to specify that the genetic vector comprises:

> (1) distal 5' flanking sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found between 20 bp and 100,000 bp 5' of a transcriptional initiation site of a ferritin heavy chain locus;
> (2) proximal 5' regulatory sequences comprising a sequence of at least 20 bases having at least 70% identity to a nucleotide sequence found between 1 bp and 10,000 bp 5' of a translational initiation codon of a ferritin heavy chain locus; *and*
> (3) proximal 3' regulatory sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found within the proximal 3' regulatory sequences of a ferritin heavy chain gene locus.

Rejected claims 46-49 depend from claim 22 and further specify the length of the first insertion site for a first heterologous coding sequence. Applicant will address the rejection in the event the Examiner may find it applicable to the claims as amended.

As described above, Perkins *et al.* does not describe 3' regulatory regions for the ferritin heavy chain gene locus, let alone the claimed proximal 3' regulatory sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found within the proximal 3' regulatory sequences of a ferritin heavy chain gene locus. Furthermore, Perkins *et al.* does not describe the lengths of the insertion sites specified in the claims.

Eglitis *et al.* describes retroviral vectors comprising a multiple cloning site with certain restriction enzyme recognition sites. *See* Eglitis *et al.* at column 6. Hillgenberg *et al.* describes viral vectors comprising a cloning site, such as a multiple cloning site or DNA with restriction cleavage sites. *See* Hillgenberg *et al.* at paragraph [0026], pages 2-3. As such, neither Eglitis *et al.* nor Hillgenberg *et al.* remedy the deficiency of Perkins *et al.* because neither Eglitis *et al.* nor Hillgenberg *et al.* describe 3' regulatory regions for the ferritin heavy chain gene locus, let alone the claimed proximal 3' regulatory sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found within the proximal 3' regulatory sequences of a ferritin heavy chain gene locus. Furthermore, neither Eglitis *et al.* nor Hillgenberg *et al.* describe or suggest the lengths of the insertion sites specified in the claims.

For at least the reasons presented above, Applicant submits that a *prima facie* case of obviousness has not been established. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

D. Perkins et al., in view of German et al. or Huston et al.

In the Office Action at pages 10-11, claims 31-32 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Perkins *et al.*, in view of German *et al.* (U.S. Patent No. 6,225,290) or Huston *et al.* (U.S. Patent No. 6,207,804). As described above, independent claim 22 has been amended to specify that the genetic vector comprises:

> (1) distal 5' flanking sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found between 20 bp and 100,000 bp 5' of a transcriptional initiation site of a ferritin heavy chain locus;
> (2) proximal 5' regulatory sequences comprising a sequence of at least 20 bases having at least 70% identity to a nucleotide sequence found between 1 bp and 10,000 bp 5' of a translational initiation codon of a ferritin heavy chain locus; *and*
> (3) proximal 3' regulatory sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found within the proximal 3' regulatory sequences of a ferritin heavy chain gene locus.

Rejected claims 31-32 depend from claim 22 and further specify that the proximal 5' regulatory sequences include a eukaryotic intron sequence. Applicant will address the rejection in the event the Examiner may find it applicable to the claims as amended.

As described above, Perkins *et al.* does not describe 3' regulatory regions for the ferritin heavy chain gene locus, let alone the claimed proximal 3' regulatory sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found within the proximal 3' regulatory sequences of a ferritin heavy chain gene locus. Furthermore, Perkins *et al.* does not describe a proximal 5' regulatory sequence that includes a eukaryotic intron sequence.

German *et al.* and Huston *et al.* fail to remedy the deficiency of Perkins *et al.* because German *et al.* and Huston *et al.* do not describe or suggest 3' regulatory regions

for the ferritin heavy chain gene locus, let alone the claimed proximal 3' regulatory sequences comprising a sequence of at least 100 bases having at least 70% identity to a nucleotide sequence found within the proximal 3' regulatory sequences of a ferritin heavy chain gene locus.

For at least the reasons presented above, Applicant submits that a *prima facie* case of obviousness has not been established. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

III. Rejection under 35 U.S.C. § 112, first paragraph

At page 11 of the Office Action, the Examiner rejected claim 64 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner alleged that pFerX11 is not supported by the application and, therefore, is new matter. *See* Office Action at page 11. Applicant respectfully traverses the rejection.

Example 3 and Table 5 describe the pFerX11 vector. *See, e.g.*, paragraphs [0107]-[0108] at page 28 of the specification. Specifically, pFerX11 is a modified version of the pFerX8 vector, wherein bases 13727-17636 of the 3' region of pFerX8 have been deleted. *See, e.g.*, Table 5. As such, Applicant submits that pFerX11 is supported by the application and respectfully requests that the Examiner withdraw this rejection.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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